Can nebivolol be helpful in Behçet's disease?

Behçet hastalığına nebivolol yararlı olabilir mi?

Behçet's disease (BD) is a chronic systemic vasculitis characterized by recurrent oral and genital ulceration, ocular and skin lesions and cardiovascular involvement about in 7-31% of cases (1, 2). It has high prevalence in countries such as Turkey, Iran and Japan (1). Although little is still known about BD's etiopathology, a correlation between genetic intrinsic factors and triggering extrinsic factors has been supposed (3). In particular, immuno-mediatory mechanism and inflammatory mediators can play an important role (4). In the last years, scientific data was focused on the inflammatory pattern of BD (5), because of the specific histopathological vasculitis pattern characterized by prominent neutrophil and monocyte infiltration in perivascular regions (6). Moreover, high concentration of pro-oxidants and lipid peroxidation products (7), high levels of oxygen-derived-free radical, serum concentration of von Willebrand factor, plasminogen activator inhibitor-1 and thrombomoduline were found in patients with BD (8, 9). On the bases of these results, a relation between oxidative stress and vascular involvement has been hypothesized in patients with BD (10). In particular, endothelial nitric oxide (NO) activity could be impaired in patients with BD lead to endothelial dysfunction. Indeed, Chambers et al. (10) reported that vascular disorders in BD are associated with a decreased activity of endothelial-derived NO.

Reduced NO activity may cause vasoconstriction, platelet aggregation and monocyte adhesion with a consequent vascular damage (11).

In the prospective single arm study published in this issue of the Anatolian Journal of Cardiology, Karakaş et al. (12), report the effect of nebivolol on endothelial dysfunction of 35 patients with BD. Although the exclusion criteria limited the study to a low risk population (clinically inactive phase of disease, no history of ischemic heart disease, heart/renal/ liver failure, no vascular disease), the authors found a significant improvement in endothelial function after a 3 months treatment with nebivolol.

The brachial artery flow-mediated dilatation (FMD) and nitrate-mediated endothelium-independent dilatation (NMD) were evaluated at baseline and after 3 months therapy with 5 mg daily of nebivolol. They found a significant improvement in FMD (4.23±1.19 vs. 7.95±2.21%, $p<0.001$) and NMD (6.52±1.69 vs. 10.16±2.31%) after treatment. Moreover there was also an improvement in the brachial artery basal lumen diameter (3.10±0.61 vs. 3.16±0.52 mm, $p<0.05$), in the post-flow brachial artery lumen diameter (3.23±0.65 vs 3.41±0.54 mm, $p<0.001$) and in brachial artery lumen diameter after nitrate administration (3.30±0.65 vs 3.48±0.57 mm, $p<0.001$). These results, even if impressive, should be interpreted taking into account some important limitations of the study. First of all the design of the study without a placebo group, the small sample size and, moreover, the NO concentration was not evaluated before the treatment and at follow-up. However, praise must be given to the authors, because this is the first report on the effect of nebivolol in patients with BD and could have an important impact on the therapeutic approach of BD patients.

Why could nebivolol be helpful in BD patients? Because it has a pharmacologic profile different from other agents if its class (β-blockers) (13). It is a third generation β-adrenergic receptor antagonist, a lipophilic β 1-AR antagonist, without effect on α-receptors, currently used in patients with coronary artery disease, hypertension and heart failure (14). Nebivolol is a racemic mixture of two isomers, d-nebivolol and l-nebivolol (15) and it has pronounced vasodilator properties by interaction with the endothelial L-arginine/nitric oxide pathway (16). In particular, these latter properties, specific of l-enantiomer, are attributed to direct stimulation of endothelial-dependent NO release with a consequent increase of NO bioavailability (17). Moreover, nebivolol reduces superoxide anion and inhibits ADP and collagen-induced platelet aggregation decreasing thrombotic risk (18).

These peculiar characteristics of nebivolol could be useful in the treatment of the vascular disorders of BD. The increase of NO bioavailability obtained with nebivolol therapy could reduce the oxidative-stress, vasoconstriction, platelet aggregation and monocyte adhesion observed in endothelial dysfunction of BD.

In conclusion, the use of drugs that improve endothelial dysfunction could open a new frontier in the treatment of patients with BD. However, it is necessary to confirm these promising data on a more extensive population with double -arm randomized controlled trial.

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